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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,649	01/28/2002	Johannes Gerdes	3276.1000000	2383

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	11

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,649	GERDES ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-48* is/are pending in the application.

4a) Of the above claim(s) *32-38, 40-42, and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-31, 39, and 43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7&8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 25-48 are pending.

2. Applicant's election with traverse of Group I, claims 25-31, 39 and 43-47 drawn to a monoclonal antibody specific for human Mcm3, filed on 9/10/02, is acknowledged.

Applicant's traversal is on the grounds that the special technical feature common to each of Groups I-IV is a monoclonal antibody specific for human Mcm3 and the teachings of the cited references would not have established the monoclonal antibodies specific for human Mcm3 of the present invention. Furthermore, the cited references, either alone or in combination, would not have reasonably suggested a monoclonal antibody specific for human Mcm3 to one of ordinary skill in the art.

Examiner agree with applicant's assertion that polyclonal antibodies are structurally and functionally different from monoclonal antibodies and polyclonal antibody can bind a multiplicity of different epitopes on the immunizing antigen, while monoclonal antibodies bind to a specific epitope. However, antibodies that bind the same or nearly the same epitopes would meet the claimed antibody specificities. Furthermore, the issue is the obviousness for one ordinary skill in the art at the time of the invention was made to use the same HsMcm3 peptide taught by Tsuruge *et al* to make monoclonal antibodies as taught by the '500 patent. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144. Here, it was not necessary for the prior art to know the applicant's recitation of specific for Mcm3 to achieve monoclonal antibodies that bind human Mcm3.

Therefore, Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 32-38, 40-42 and 48 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 25-31, 39 and 43-47 are under examination.

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. Applicant's IDS, filed 2/22/02, 2/25/02 and 5/3/02 (Paper Nos. 6, 7 and 8), is acknowledged, however, the references cited in the Search Report of PCT/US00/02910 have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed within the set period for reply to this Office Action.

7. The use of the trademark "SurfZAP®", page 7, line 35 and "CELLocate®" page 20, line 1, has been noted in this application. It should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

8. The disclosure is objected to because the "Mcm3" page 5 line 35, "MCm3" page 5, line 14, "McM3" page 5 line 12, and "MCM3" in page 14, line 36 are used interchangeably. Consistency is required.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 26 is indefinite in the recitation of "same properties". It is unclear what properties are contemplated.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 25-29, 31, 39 and 43-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> It is apparent that the hybridoma DSM ACC2388 that produce the monoclonal antibody specific for human Mcm3 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.
>
> If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of the patent whichever is longer*. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature much be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

Further, the specification does not reasonably provide enablement for a method for the production of a preparation for the therapy of tumors, allergies, autoimmunopathies, scar formation, inflammation and rheumatic diseases as well as the suppression of defense reactions of transplantations employing the monoclonal antibody specific for human Mcm3 in claim 44, any pharmaceutical composition comprising any monoclonal antibody specific for human Mcm3 together with a pharmaceutical acceptable adjuvant in claim 45. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Also, at issue is whether or not the claimed pharmaceutical composition and preparation for the therapy would function to treat "tumors, allergies, autoimmunopathies, scar formation, inflammation and rheumatic diseases as well as the suppression of defense reactions of transplantations". The specification discloses the microinjection of anti-Mcm3 antibodies in the nuclei of permanent cell line cells resulted in inhibition of cell proliferation. The exemplification is drawn to the inhibition of cell proliferation, in vitro model of microinjection (pages 19-21).

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since no animal was used as model system to treat tumors, allergies, autoimmunopathies, scar formation, inflammation and rheumatic diseases as well as the suppression of defense reactions of transplantations. It is not clear that reliance on in vitro model to inhibit cell proliferation accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively reach any therapeutic endpoint in mammals by administrating the therapeutic preparation/pharmaceutical composition. The specification does not teach how to extrapolate data obtained from in vitro model of inhibiting cell proliferation studies to the development of effective in vivo mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the preparation for the therapy/ pharmaceutical composition exemplified in the specification.

However, an effective protocol for the treatment against tumors, allergies, autoimmunopathies, scar formation, inflammation and rheumatic diseases as well as the suppression of defense reactions of transplantations in mammalian is subject to a number of factors which enter the picture beyond simply the administration of the pharmaceutical composition in an acceptable formulation. Demonstrating inhibition in cell proliferation cannot alone support the predictability of the method for treating against said disorders through administration of the appropriate formulation. The ability of a host to suppress and thereby treat against said diseases will vary depending upon factors such as the condition of the host and burden of disease.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 25, 26, 28, 30, 39, 43- 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuruga *et al* (of record) in view of Harlow *et al* 1989 and U.S. Patent 5,876,438.

Tsuruga *et al* teach polyclonal antibodies (MBL) to synthesized peptides (EEEKSQEDQEQKRKRRKTRQPDAK) corresponding to residues No. 677-700 of human Mcm3 (HsMcm3) (see page 119, right column, 2nd paragraph in particular). Tsuruga *et al* further teach that the amino acid sequence of the peptide is only found in HsMcm3 protein from which the sequence was derived and hence that the antibody would only react with human Mcm3. Tsuruga *et al* teach that antibodies against HsMcm3 were monospecfic, recognizing only a single band at the expected size on SDS-PAGE gels (see page 119, right column, 2nd paragraph and page 20 FIG. 1 in particular). Finally, Tsuruga et al teach the antibody in TBST buffer (page 119, under Immunoprecipation and Western blot analyses in particular).

The claimed invention differs from the reference teachings only by the recitation of monoclonal antibody in claim 1, wherein the monoclonal antibody altered biochemically, by molecular biology or synthetically in claim 28, a process for the production of the antibody according to Claim 25, characterized in that an animal is immuninized with human Mcm3, and monoclonal antibodies are obtained after fusion of spleen cells of the animal with myeloma cells which comprises the steps: (i) initial screening of the hybridoma by means of an immunobiochemical method; (ii) screening of the hybridoma that were positive in step (i) by means of an immunohistochemical method in claim 39, A diagnostic composition comprising a monoclonal antibody specific for human Mcm3 in claim 43, a method for the production of a preparation for the therapy of tumors, allergies, autoimmunopathies, scar formation, inflammation and rheumatic diseases as well as the suppression of defense reations of transplantions employing the monoclonal antibody in claim 44, a pharmaceutical composition comprising a monoclonal antibody specific for human Mcm3 together with a pharmaceutical acceptable adjuvant in claim 45.

Harlow et al teach a method of producing monoclonal antibodies comprising immunizing an animal (i.e. a mouse) with a protein or portion thereof (i.e. fragments), harvesting spleen cells from said animal, fusing said spleen cells with myeloma cell line, and culturing said fused cells (i.e hybridoma) under conditions that allow production of said antibody. Harlow *et al* further teach that the monoclonal antibodies stems from their specificity, homogeneity and ability to be produced in unlimited quantities (see pages 141-157 in particular).

The `438 patent teaches that to identify hybridomas producing monoclonal antibodies of interest with the desired specificity, antibodies secreted by the immortalized cells are screened to identify the clones that secrete antibodies of the desired characteristics. Screening of the hybridoma clones can be performed by radioimmunoassay and immunohistochemical staining . The `438 patent further teaches the monoclonal antibodies can be modified by truncating the constant region by various peptidase digestions. The monoclonal antibodies can be reduced to provide for Fab fragments with available mercaptan sites for conjugation to other compositions (column 7 lines 33-44 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody using the method taught by Halow *et al* with the synthesized peptides corresponding to residues No. 677-700 taught by Tsuruga *et al* and screen the resultant hybridoma cells by radioimmunoassay and immunohistochemical staining as taught by the `438 patent.

One ordinary skill in the art at the time the invention was made would have been motivated to do so because the monoclonal antibodies produced exhibit a high degree of specificity, homogeneity and ability to be produced in unlimited quantities as taught by Halow *et al.* and the screening methods will allow the identification of the hybridoma of interest with the desired specificity as taught by `438 patent.

Claim 26 is included because a monoclonal antibody specific for human Mcm3 would have the "same properties" as the monoclonal antibody of the hybridoma cell line with the deposit number DSM ACC2388.

Claims 43 and 45 are included because Tsuruga *et al* teach an antibody composition in TBST buffer, which is also consider to be a pharmaceutically acceptable carrier and the term "pharmaceutical composition" carries little patentable weight in the absence of evidence of structural difference.

Claim 44 is included because an antibody is an antibody irrespective of its intended use.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuruga *et al* (of record) in view of Harlow *et al* 1989 and U.S. Patent No. 4,281,061.

The teachings of Tsuruga *et al* and Harlow *et al* references have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a diagnostic kit comprising the monoclonal antibody specific for human Mcm3 in claim 46.

The `061 patent teach that reagents for an immunoassay can be provided as kits as a matter of convenience and to optimize the sensitivity of the assay in the range of interest (col 22, line 62 - col 23, line 4).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody using the method taught by Halow *et al* with the synthesized peptides corresponding to residues No. 677-700 taught by Tsuruga *et al* and include the monoclonal antibody in a kit format as taught by the `061 patent.

One ordinary skill in the art at the time the invention was made would have been motivated to so because such kits are provided for a matter of convenience and to optimize the sensitivity of the assay in the range of interest as taught by `061 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuruga *et al* (of record) in view of Harlow *et al* 1989 and U.S. Patent No. 4,281,061, as applied to claim 46 above, and further in view of U.S. Patent No. 6,316,208.

The Tsuruga *et al*, Harlow *et al*. references and `061 patent, have been discussed, supra. Tsuruga *et al* further teaches characterization of HsMcm proteins, including the analysis of their expression nuclear localization during cell cycle and quiescent state (see page 119, 1st paragraph in particular).

The claimed invention differs from the reference teachings only by the recitation of a diagnostic kit for the combined detection of expression of Mcm3, Ki-67 and p27 for tumor diagnosis in claim 47.

The `208 patent teaches antibodies p27 and Ki-67 used for immunostaining (column 46 lines 18-22 in particular). The `208 patent further teaches that the antibodies were used for histologic grade and assays of p27, Ki-67 proliferation index in tumor cells and expresion level (column 44 lines 13-29 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody using the method taught by Halow *et al* with the synthesized peptides corresponding to residues No. 677-700 taught by Tsuruga *et al* and combined the monoclonal antibody Mcm3 with antibodies Ki-67 and p27 taught by as taught by the `208 patent in a diagnostic kit as taught by the `061 patent.

One ordinary skill in the art at the time the invention was made would have been motivated to do so because the combined Mcm3 antibody with the antibodies p27 and Ki-67 to characterize the proliferation of tumor cells as taught by the `208 patent and the expression nuclear localization of Mcm3 during cell cycle as taught by Tsuruga *et al*.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

17. **1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
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November 18, 2002

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